Remarks

Claims 1, 4-6, 13, 17, and 31-48 are pending and now before the Examiner for consideration; claims 35-47 are withdrawn from consideration. Claims 6, 31, and 35 to 47 have been canceled in the amendment of this date. Certain of the claims have been amended for the purpose of expediting the patent application process in a manner consistent with the Patent and Trademark Office Patent Business Goals (PBG), 65 Fed. Reg. 54603 (September 8, 2000), in order to lend greater specificity to the claimed subject matter, advance prosecution, and facilitate the business interests of Applicant(s). Support for these new claims and the amendments to the pending claims can be found throughout the subject specification, including, for example, the originally filed claims and description (see, for example, pages 5-8 and page 18, about line 15). Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Claims 4-6 have been rejected under U.S.C. § 112, first paragraph, as containing subject matter not described in the specification. Specifically, the Examiner alleges that the following claim limitations do not find support in the instant specification:

1. the "site that is cleaved *in vivo*" recited in claim 4, as the site does not have to be in between T cell epitopes;
2. "or immunostimulatory fragments of SEQ ID NO: 1, 2, or 3" recited in claim 6; and
3. "DRB1*1501" and "DRB1*0901" recited in claim 33.

Applicants respectfully submit that the claim limitations are supported by the originally presented specification as follows. For example, support for the "site that is cleaved *in vivo*" is found in the originally filed specification at page 8, lines 3-14, which states that:

> "In this peptide, a region that is cleaved in vivo is preferably inserted between the T-cell epitope containing peptides to minimize the occurrence of epitope sites that are newly recognized. The multi-epitope peptide is finally broken

down to the respective antigenic peptides at the cleavage site. The cleavage site may take any structure so long as it undergoes cleavage in vivo."

Although it is preferable that the cleavage site be positioned between T cell epitopes, the specification indicates that such is merely preferable and not required. With regard to item 2, claim 6 has been cancelled, thus rendering this rejection moot. Applicants further respectfully submit that support for the limitation identified in item 3 is found in the originally filed specification at page 2, lines 12-15 and page 24, lines 12, 15, 18, and 21 as well as Figure 3 (T cell clone PB9-34), Figure 4 (T cell clones PB5-29, PB12-33, PR1-20, PB5-2, PR2-34) and Figure 6. Accordingly, reconsideration and withdrawal of the new matter rejection is respectfully requested.

Claims 1, 4-6, 13, 17, 31-34, and 48 have been rejected under 35 U.S.C. § 103(a) as being obvious over Rogers in view of WO94/01560, and further in view of Hashiguchi *et al.* or Komiyama *et al.* or WO94/11512 or Wallner *et al.* or Rammensee *et al.* According to the Examiner, Rogers *et al.* teach a multi-epitope immunotherapeutic polypeptide, wherein said T-cell epitopes are derived from different allergen molecules. Rogers et al. fails to provide any teaching related to cedar pollen antigens Cry j 1 and/or Cry j 2. Particularly, Rogers *et al.* do not teach (a) the specific epitopes recited in claim 1, namely the recited epitopes (epitope peptides) obtained from cedar pollen allergens Cry j 1 and Cry j 2; (b) the insertion of a cleavage site between the epitopes, such as an arginine or lysine dimer, as is required by claims 4 and 5; (c) T cell epitopes restricted by one of HLA class II DR, DQ, DP as is required by claims 32 and 33; or (d) T cell epitopes comprising analog peptides in which one or more amino acid residues are substituted, as is required by claim 48.

The Office Action seeks to remedy the deficiencies of the reference by citing WO 94/01560 (Immunologic Pharmaceutical Corporation, hereinafter "IPC I"), WO 94/11512 (herein after referred to as "IPC II"), Hashiguchi, and Komiyama *et al.* IPC I is cited for its disclosure of a linear polypeptide comprising at least two different epitope regions from Cry j 1, the use of charged amino acid pairs for the introduction of protease cleavage sites, amino acid substitutions to enhance stability and effectiveness. WO 94/11512 (IPC II), Hashiguchi, and Komiyama *et al.* are cited for teaching the purified Cry j 2 protein and T cell epitopes thereof and the use of same to treat, diagnose and prevent

Japanese cedar pollinosis. Finally, Rammensee *et al.* is cited for teaching haplotypes of HLA-DR, DQ, and DP and peptides that bind to them, including DRß5-0101.

The Office Action concludes that it would have been obvious to one of ordinary skill in the art to combine the teachings of these six references to arrive at Applicants' claimed invention. Specifically, the Office Action argues that one could have made the multi-epitope immunotherapeutic agent of Rogers *et al.*, by linking the Cry j 1 peptides disclosed by IPC I to the Cry j 2 peptides disclosed by Hashiguchi, Komiyama or IPC II. The Office Action goes on to suggest that the inclusion of dimeric cleavage sites, specific epitopes restricted by HLA class, and amino acid substitutions would have been obvious in view of the cited teachings.

Applicants also wish to point out that the major allergen from the domestic cat, *Fel d 1*, is a heterodimeric protein comprised of two disulfide linked polypeptide chains, dubbed chain 1 and chain 2. Rogers teaches the "construction and characterization of recombinant proteins that contains various configurations of multiple T cell epitopes derived from each of the two chains of the *Fel d 1* allergen." See p. 956, col. 2 - emphasis added. Accordingly, although the Rogers' immunopeptides contain multiple epitopes, these "multiple" epitopes are isolated from a ***single allergen*** (*Fel d 1*) and not from two ***different allergens*** (*Cry j 1* and *Cry j 2*) as is required by the present claims. Thus, the Examiner's statement that "Rogers et al. teach a peptide-based immunotherapeutic agent comprising a linear multi-epitope polypeptide with different T cell epitopes joined to each other . . . wherein said different T cell epitope regions are derived from two or more different allergen molecules" is incorrect.

Applicants further submit that WO 94/01560 focuses exclusively on the Cry j I allergen and functional fragments thereof. WO94/11512, filed 10 months later by the same company, focuses exclusively on the Cry j 2 allergen and functional fragments thereof. Both disclosures are limited to single allergen therapeutics. Neither document suggests that the two distinct cedar pollen allergens may be combined in any way (e.g., co-administered as separate dosages), much less that they can be combined into a single linear peptide molecule as is claimed. The fact that such a disclosure is

absent undermines the Examiner's conclusion that the claimed peptide molecules would have been obvious one of ordinary skill in the art.

Finally, it is respectfully submitted that none of the cited references, either alone or in combination, suggest a linear polypeptide molecule comprised of T-cell epitope peptides derived from ***different allergens***, much less comprised of at least two T-cell epitope peptides derived from cedar pollen allergen Cry j 1 and at least two T-cell epitope peptides derived from cedar pollen allergen Cry j 2 as is required by independent claim 1.

As the Patent Office is aware, all the claim limitations must be taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). It is respectfully submitted that the references fail to teach the invention presented in the presently claimed invention. Particularly, the references fail to teach one or more T-cell epitope peptides selected from the group consisting of peptide nos. 14, 15, 16, 17, 22 and 43 of cedar pollen allergen Cry j 1 as set forth in Fig. 1 linearly bound to one or more T-cell epitope peptides selected from the peptide group consisting of peptide no. 14, 17, 18, 37, 38, 48 and 69 of Cry j2 as set forth in Figure 2. Furthermore, when a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). In the case of the instant invention, there is no teaching or suggestion to combine the claimed peptides into a linear multi-epitope construct as set forth in the claims. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Additionally, the mere fact that references can be cobbled together to yield a claimed invention is not dispositive of the issue of obviousness. In this case, the Examiner has found bits and pieces of the invention in the literature and summarily concluded that the invention is obvious. Such piecemeal analysis is improper and contrary to the explicit instructions of the law, particularly MPEP § 2142.02, which specifically directs Examiner's to consider the invention as a whole. Distilling the invention down to a "gist" or "thrust", as the Examiner has done here, disregards this directive.

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In view of the foregoing remarks and the amendments to the claims, the applicant believes that the pending claims are now in condition for allowance, and such action is respectfully requested. The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

DRAFT

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Attachments: Marked-Up Version of Amended Claim
Petition for Two-Month Extension of Time

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Docket No. SPO-103
Serial No. 09/142,524

Marked-Up Version of Amended Claim

Claim 1. (Fourth Amendment)

A peptide-based immunotherapeutic agent for cedar pollinosis comprising an effective amount of a polypeptide, wherein said polypeptide:

(a) ~~comprises at least two T-cell epitope peptides derived from cedar pollen allergen Cry j 1 and at least two T-cell epitope peptides derived from cedar pollen allergen Cry j 2;~~is a polypeptide in which (i) at least one T-cell epitope peptide comprising an amino acid sequence selected from the peptide group consisting of peptide no. 14 (SEQ ID NO: 28), 15 (SEQ ID NO: 29), 16 (SEQ ID NO: 30), 17 (SEQ ID NO: 31), 22 (SEQ ID NO: 36) and 43 (SEQ ID NO: 57) of cedar pollen allergen Cry j 1 shown in Fig. 1, is linearly bound to (ii) a T-cell epitope peptide comprising an amino acid sequence selected from the peptide group consisting of peptide no. 14 (SEQ ID NO: 97), 17 (SEQ ID NO: 100), 18 (SEQ ID NO: 101), 37 (SEQ ID NO: 120), 38 (SEQ ID NO: 121), 48 (SEQ ID NO: 131) and 69 (SEQ ID NO: 152) of cedar pollen allergen Cry j 2 shown in Fig. 2,

~~(b) is capable of inducing proliferation of T-cell clones specific to each of said T-cell epitope peptides; and~~

~~(c) is capable of dose-dependently inducing proliferation of peripheral lymphocytes from a cedar pollinosis patient.~~

(b) does not substantively bind to cedar pollen allergen-specific IgE antibody in serum of cedar pollinosis patients,

(c) is capable of proliferating *in vitro* human T cell clones specific to the T cell epitope peptide within the peptides of (a)

(d) is capable of proliferating *in vitro* peripheral blood lymphocytes of a cedar pollinosis patient, and

(e) has no cysteine residues.